

# Small Cell Lung Cancer in a 20-year-old Non-Smoking Man with Systemic Sclerosis

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## Abstract

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Small cell lung cancer (SCLC) is a neuroendocrine tumor, and the median age of onset is about 70 years old. A 20-year-old non-smoking man with known systemic sclerosis presented with discomfort in his left chest. Chest X-ray showed a mass shadow in the left upper zone. A transbronchial lung biopsy revealed small cell carcinoma, and imaging studies reached the diagnosis of extensive disease small cell lung cancer. He had concurrent interstitial lung disease with a non-specific interstitial pneumonia pattern and anti-Scl-70 antibodies. He died eight months after the diagnosis during fifth-line chemotherapy. We herein report the youngest case to date of SCLC with systemic sclerosis.

**Key words:** small cell lung cancer, systemic sclerosis, non-smoker, 20-year-old

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## Introduction

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Small cell lung cancer (SCLC) is a tumor of neuroendocrine origin (1), accounting for over 10% of all lung cancers (2). The median age of onset is about 70 years (3). SCLC has a close association with tobacco smoking (4), with over 95% of SCLC patients being smokers (5). Systemic sclerosis (SSc) is a risk factor for the development of all cancers, although it is most closely associated with lung cancer (6).

We herein report a rare case of a 20-year-old non-smoking man with known SSc who developed SCLC.

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## Case Report

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A 20-year-old Japanese man who had been diagnosed with SSc at the age of 17 presented to our department with discomfort in his left chest.

His earliest symptom of SSc was Raynaud's phenomenon, at the age of eight. At age 12, he developed sclerodermatous changes in his hands. He had experienced pneumothorax 4 times since age 14. At 17, he was diagnosed with SSc based

on systemic sclerodermatous skin changes and a loss of substance of the distal finger pads. He was positive for anti-Scl-70 antibody, and a histological re-examination of a resected lung specimen for treatment of pneumothorax revealed non-specific interstitial pneumonia (NSIP). Due to the lack of any organ complications, immunosuppressants were not prescribed.

The patient was an undergraduate university student who had never smoked and had no history of exposure to known carcinogens, nor any family history of malignancy. On a physical examination, we detected no abnormalities except for widespread sclerodermatous changes to the head, trunk and limbs.

Laboratory tests showed a white blood cell count of  $4.6 \times 10^9/L$  with a normal differential count, lactate dehydrogenase (LDH) 256 U/L, Krebs von den Lungen-6 (KL-6) 631 U/L, C-reactive protein (CRP) 0.14 mg/dL, carcinoembryonic antigen (CEA) 2.0 ng/mL, cytokeratin-19 fragments (CYFRA) 2.3 ng/mL, neuron-specific enolase (NSE) 92.6 ng/mL, and pro-gastrin-releasing peptide (ProGRP) 170 pg/mL. Serum cryptococcus antigen, aspergillus antigen,  $\beta$ -D glucan, anti-RNA polymerase III antibody, and anti-centromere antibody were negative.

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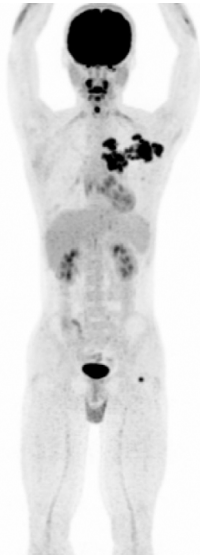
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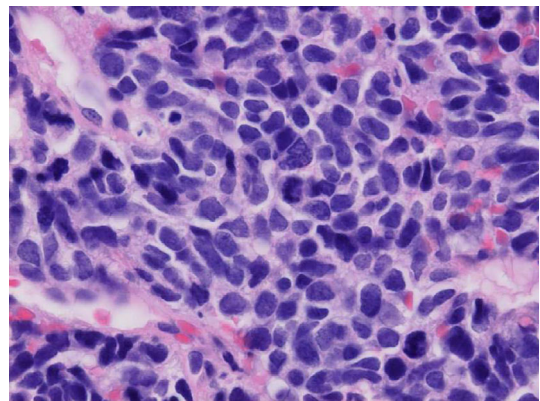
**Figure 1.** Chest X-ray showed a mass shadow in the peripheral area of the left upper zone, and widespread diffuse reticular shadows.



**Figure 2.** A computed tomography (CT) scan of the chest revealed a mass in the left upper lobe (S3; 4.1×6.4×4.5 cm) with features suggestive of pleural infiltration, and marked enlargement of the left hilar, superior mediastinal, para-aortic, and axillary lymph nodes. There was a separate left para-spinal mass (4.3×3.0 cm) progressing into the vertebral canal at the Th5 vertebral level. There were also upper lobe dominant cystic spaces.



**Figure 3.** PET-CT revealed high accumulation in the left upper lobe mass (standardized uptake value max: SUVmax 9.5) (Fig. 3), the left para-spinal mass (SUVmax 10.4), enlarged lymph nodes, and the left femoral head (SUVmax 8.0)

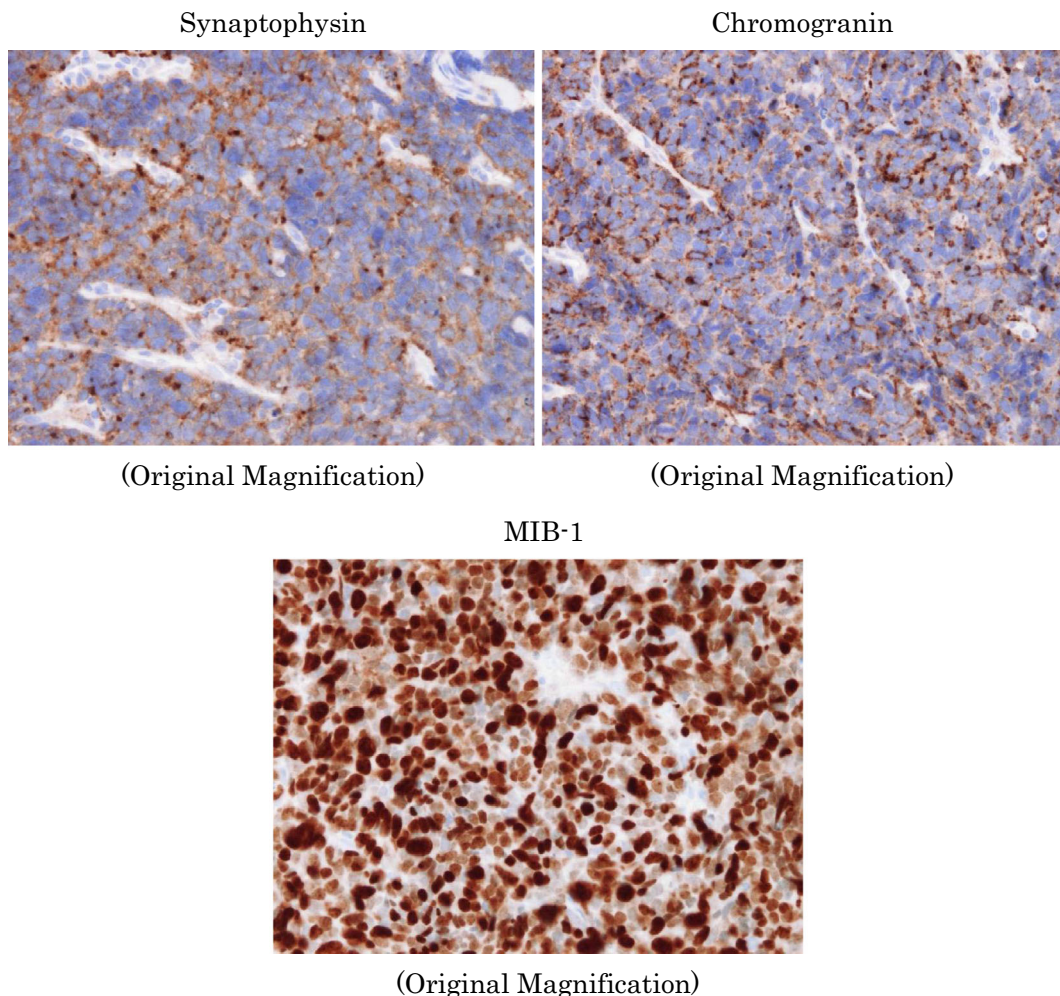


**Figure 4.** A transbronchial biopsy of the left upper lobe mass revealed small-sized tumor cells possessing minimal cytoplasm and hyperchromatic indistinct nucleoli with abnormal mitosis. (Original Magnification)

Chest X-ray showed a mass shadow in the peripheral area of the left upper zone (Fig. 1). A computed tomography (CT) scan of the chest revealed a mass in the left upper lobe, with pleural infiltration, enlarged lymph nodes, and a left paraspinal mass. There were upper-lobe dominant cystic spaces that were considered to be pathologically correlated with progressive-stage interstitial lung disease (ILD) (Fig. 2). On lung function tests, the percent predicted volume capacity (%VC) was 55.3%, and the forced expiratory volume percentage in 1 second (forced expiratory volume (FEV) 1.0%) was 94.7%. Positron emission tomography (PET)-CT revealed high accumulation in the left upper lobe mass, the left paraspinal mass, the enlarged lymph nodes,

and the left femoral head (Fig. 3). CT, PET-CT, and magnetic resonance imaging (MRI) of the brain revealed no metastatic lesions to any organs except the left femoral head. A transbronchial lung biopsy of the left upper lobe mass revealed small cell carcinoma with neuroendocrine characteristics (Fig. 4, 5). Based on these findings, he was diagnosed with extensive-disease SCLC (T3N2M1b, clinical staging).

Chemotherapy was commenced with cisplatin (80 mg/m<sup>2</sup> on day 1) plus etoposide (100 mg/m<sup>2</sup> on days 1-3). The left para-spinal mass had progressed into the vertebral canal, nearly invading the spinal cord. Therefore, we performed concurrent bilateral irradiation to the paravertebral mass of 30 Gray (Gy) in 10 fractions over 12 days. The tumor responded to the first cycle of the chemotherapy without adverse events of grade 3 or more, but after 4 cycles, the tumor progressed. As second-line chemotherapy, we avoided



**Figure 5.** Immunohistochemical staining revealed that the tumor cells were positive for chromogranin A, synaptophysin, and thyroid transcription factor-1 (TTF-1), and negative for p40. Ki-67 antigen (MIB-1) labeling index was 96%.

irinotecan and amrubicin, which can easily cause exacerbation of ILD, and chose topotecan therapy (1 mg/m<sup>2</sup> on days 1-5). However, after two weeks the enlarged left hilar lymph nodes caused constriction of the left main bronchus, and head MRI revealed three brain metastatic lesions. External beam therapy in 4-field box treatment to the lymph nodes (30 Gy in 10 fractions over 15 days) and gamma knife therapy (margin dose: 18 Gy) were performed with 8 mg/day dexamethasone. After radiotherapy, he received weekly paclitaxel therapy (80 mg/m<sup>2</sup> on days 1, 8, and 15) as third-line chemotherapy. During the third course, head MRI revealed multiple new brain metastases, and cranial irradiation (30 Gy in 10 fractions over 14 days) was given. Vinorelbine therapy (25 mg/m<sup>2</sup> on days 1, 8, and 15) as fourth-line chemotherapy resulted in progressive disease, so he began S-1 therapy (50 mg/dose, twice a day on days 1-28) but eventually died of respiratory failure 8 months after the diagnosis. Consent for autopsy could not be obtained.

## Discussion

SCLC is uncommon in the young (7, 8). SCLC in SSc

patients is considered to be rare, but the incidence rate is unclear (9-11). Furthermore, SCLC among non-smokers is very rare (5, 12). To our knowledge, the youngest cases with SCLC are a 14-year-old boy and a 14-year-old girl in the literature (13, 14), but to our knowledge, this is the youngest case of SCLC in an SSc patient. Several reports have described the characteristics of lung cancer in patients with SSc (6, 15, 16); the proportion of women is higher than in the general population, and the most frequent pathological type is adenocarcinoma. SCLC is known to have more gene mutations than non-SCLC in non-smokers (17); it is therefore possible that there were some additional triggers influencing the development of SCLC in such a young non-smoker.

The development of lung cancer in SSc patients has long been considered to be associated with pulmonary fibrosis (6). It has been reported that idiopathic pulmonary fibrosis (IPF) patients have an increased risk of lung cancer (18, 19), but the relationship between other types of ILD and lung cancer is unclear.

Several reports have discussed the possible relationship between autoantibodies and cancer (20-23). In our case, the

patient had anti-Scl 70 antibody. Foeldvari et al. reported that, in a group of SSc patients with a young onset, the rate of anticentromere antibody positivity was low (21). Colaci et al. reported that anti-Scl-70 antibodies are associated with an increased risk of developing lung cancer in Italy (15). In contrast, Shah et al. stated that patients with anti-Scl-70 antibody or anti-centromere antibody positivity tended to have a longer interval between the SSc onset and the cancer diagnosis (22), whereas this interval was relatively short among SSc patients with autoantibodies to RNA polymerase I/III. Furthermore, Joseph et al. showed that SSc patients with autoantibodies to RNA polymerase III subunit (RPC1) often develop cancer before the onset of SSc (23). Interestingly, this study suggests that cancer can induce the development of anti-RPC1 antibody-positive SSc. In other words, cancer itself can induce autoimmune disease through autoantibodies.

In our case, the patient had anti-Scl-70 antibody, not anti-RPC1 antibody, and he developed SCLC 12 years after the onset of SSc. In addition, the hypothesis that SSc patients can develop cancer through a specific autoantibody has not been demonstrated to date. However, given that cancer can induce the development of autoimmune disease through a specific autoantibody, it may be possible that autoimmune disease can induce the development of cancer through a specific autoimmunity.

In conclusion, we were unable to determine the mechanisms by which our young non-smoker developed SCLC. This highlights the importance of performing a molecular biological analysis, such as detecting genetic defects using a next-generation sequencer, in such rare cases in order to gain further insight about the development of cancer and autoimmune diseases and the relationship between these complex disorders.

**The authors state that they have no Conflict of Interest (COI).**

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